DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Xeris Pharmaceuticals, Inc.
Attention: Michele Yelmene
Vice President, Global Regulatory Affairs & Operations
900 Northbrook Drive, Suite 200
Trevose, PA 19053

RE: NDA 214133
RECORLEV (levoketoconazole) tablets, oral
MA 14

Dear Michele Yelmene:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the promotional communications, the "What is Recorlev®?" and "Taking Recorlev®" webpages[1] of the consumer website (US-REC-21-00033 [v1.0]) (webpages) for RECORLEV (levoketoconazole) tablets, oral (Recorlev) submitted by Xeris Pharmaceuticals, Inc. (Xeris) under cover of Form FDA 2253. The webpages make false or misleading claims and representations about the safety and efficacy of Recorlev. Thus, the webpages misbrand Recorlev within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act), making its distribution violative. 21 U.S.C. 352(a), (n); 321(n), 331(a). See 21 CFR 202.1(e)(3)(i); (e)(5). These violations are especially concerning from a public health perspective because the promotional communications create a misleading impression regarding the safety and effectiveness of Recorlev, a drug with a number of serious and potentially life-threatening risks, including boxed warnings regarding the risks of hepatotoxicity and QT prolongation.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Recorlev.[2] According to the INDICATIONS AND USAGE section of the FDA-approved prescribing information (PI):

> RECORLEV is indicated for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative.

[1] "What is Recorlev®?" webpage located at https://www.recorlev.com/what-is-recorlev/ and "Taking Recorlev®" webpage located at https://www.recorlev.com/taking-recorlev/ (last accessed 06.05.2023).
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional communication(s) cited in this letter.

Limitations of Use
RECORLEV is not approved for the treatment of fungal infections. The safety and effectiveness of RECORLEV for the treatment of fungal infections have not been established.

The PI for Recorlev contains boxed warnings regarding the risks of hepatotoxicity and QT prolongation. Recorlev is contraindicated in patients with cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT greater than 3 times the upper limit of normal, recurrent symptomatic cholelithiasis, a prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment, or extensive metastatic liver disease; in patients taking drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes; in patients with a prolonged QTcF interval of greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history); in patients with known hypersensitivity to levoketoconazole, ketoconazole or any excipient in RECORLEV; and in patients taking certain drugs that are sensitive substrates of CYP3A4 or CYP3A4 and P-gP. In addition, the PI for Recorlev includes warnings and precautions regarding hypercortisolism, hypersensitivity reactions, and risks related to decreased testosterone. The most common adverse reactions (incidence > 20%) reported with Recorlev were nausea/vomiting, hypokalemia, hemorrhage/contusion, systemic hypertension, headache, hepatic injury, abnormal uterine bleeding, erythema, fatigue, abdominal pain/dyspepsia, arthritis, upper respiratory infection, myalgia, arrhythmia, back pain, insomnia/sleep disturbances, and peripheral edema.

False or Misleading Claims about Efficacy

Prescription drug advertisements and labeling (promotional communications) misbrand a drug if they are false or misleading with respect to efficacy. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication**.**

The "What is Recorlev®?" webpage includes the following presentation regarding the SONICS study (emphasis original):

- "**The SONICS clinical study supported the efficacy and safety results from LOGICS**"
    - "**31%** of patients had normal cortisol levels after taking Recorlev for 6 months without changing their dose"

- "**67%** of patients who moved on to the second part of the study had normal cortisol levels by the end of the study"

The claim, "**67%** of patients who moved on to the second part of the study had normal cortisol levels by the end of the study" (emphasis original), misleadingly overstates the efficacy of Recorlev. According to the CLINICAL STUDIES section of the PI, the SONICS study (Study 2) consisted of three phases (dose titration, maintenance, and extended evaluation). Out of the 94 patients who enrolled in the study and entered the dose titration phase, 77 patients "moved on to the second part of the study" (i.e., maintenance phase). At the end of the maintenance phase, only 29 of those 77 (38%) patients had normal cortisol levels. By the end of the extended evaluation phase, the number of patients with normal cortisol levels decreased to 16 of those 77 (21%) patients. We acknowledge that according to the PI, 67% of patients in the SONICS study had normal cortisol levels at the end of the titration phase; however, the titration phase was not the "end of the study." In addition, regardless of whether the end of the maintenance phase or extended evaluation phase is considered the "end of the study," both phases failed to attain the results claimed on the webpage, with 38% and 21% of patients reaching normal cortisol levels, respectively, rather than 67%. Therefore, suggesting that 67% of patients who "moved on to the second part of the study" had normal cortisol levels by the end of the study significantly overstates the efficacy of the product.

Furthermore, the presentation omits material information necessary to interpret any study results from the SONICS study (Study 2). Specifically, the CLINICAL STUDIES section of the PI states, "[b]ecause 51% of patients discontinued treatment prematurely due to adverse reaction, lack of efficacy, or other reasons, these results should be interpreted with caution." The omission of this material information from the webpage undermines the ability of the reader to understand and evaluate the study results presented and thereby creates a misleading impression about the drug's efficacy.

The "What is Recorlev®?" webpage also includes the following claim regarding the LOGICS study (emphasis original):

- "**Recorlev** - More patients (52%) who were on a stable and steady dose of Recorlev had normal cortisol levels"

This claim creates a misleading impression regarding the efficacy of Recorlev because it implies that the results represent the general experience of patients with the drug. On the contrary, the results presented are based on a small, select subset of patients enrolled in the study who had already demonstrated that they were able to tolerate and respond to the drug.

According to the CLINICAL STUDIES section of the PI, the LOGICS study (Study 1) consisted of two phases, a dose titration and maintenance phase followed by a randomized withdrawal phase. Seventy-nine patients entered the dose titration and maintenance phase. Patients who achieved a stable therapeutic dose for at least 4 weeks and achieved a normal mean urinary free cortisol (i.e., "normal cortisol levels") at the end of the dose titration and

maintenance phase were eligible for the withdrawal phase. Only 39 patients with "normal cortisol levels" entered the withdrawal phase (37 from the dose titration and maintenance phase of the LOGICS study and 2 directly from a separate study as allowed by the LOGICS study design). Over half of the patients who entered the titration and maintenance phase of the LOGICS study discontinued for various reasons, including experiencing adverse reactions and lack of efficacy. Of the 39 patients that continued to the withdrawal phase of the study, 21 were randomized to Recorlev, and 18 to placebo. It is only out of those 21 patients in the Recorlev group (from the 79 that underwent dose titration) that 52% (11/21) achieved "normal cortisol levels" at the end of the withdrawal phase. Thus, it is misleading to suggest that the results from this enriched patient population represent the general experience expected in patients who take Recorlev.

False or Misleading Risk Presentation

Promotional communications misbrand a drug if they are false or misleading with respect to risk. The determination of whether a promotional communication is misleading includes, among other things, not only representations made or suggested in the promotional communication, but also the extent to which the promotional communication fails to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the promotional communication.

The "Taking Recorlev®" webpage includes the following presentation under the header "**Monitoring and side effects**" (emphasis original):

- "**Monitoring**"

  "**As with other medicines for Cushing's, monitoring by your doctor is important so they know how you're doing**"
  . . .
  "Heart and liver tests before and during treatment with Recorlev will help your doctor avoid side effects"

- "**Possible side effects**"

  "**Side effects can occur with Recorlev, including some that are serious**"

This presentation minimizes the serious and significant risks associated with the use of Recorlev by acknowledging that "[s]ide effects can occur with Recorlev, including some that are serious," without discussing information regarding Recorlev's boxed warnings or specific side effects associated with the drug, including those that are potentially fatal. Additionally, this presentation suggests that heart and liver tests alone will enable patients to "avoid" side effects altogether. As noted above, the PI for Recorlev includes boxed warnings for hepatotoxicity and QT prolongation. The risk of hepatotoxicity has been associated with use

of oral ketoconazole[3] and has led to fatal outcomes or the need for liver transplantation. Similarly, the risk of QT prolongation associated with Recorlev has resulted in life-threatening ventricular dysrhythmias. The webpage's presentation is especially concerning given that a number of patients taking Recorlev in clinical studies experienced these potentially life-threatening side effects. For example, the WARNINGS AND PRECAUTIONS section of the PI states that 13% of patients using Recorlev experienced drug-induced liver injury, and 14.7% of patients experienced a change-from-baseline QTcF >60 msec. The PI also notes that Recorlev is associated with multiple other serious and potentially life-threatening risks unrelated to heart or liver problems, as well as numerous common adverse reactions, many of which occurred in more than 20% of patients treated with the drug.

We acknowledge that risk information for Recorlev is presented separately in the "INDICATION AND IMPORTANT SAFETY INFORMATION" section of the webpage. However, this does not mitigate the misleading impression created by the "Monitoring and side effects" presentation because the boxed warnings are relegated to the middle of this consolidated risk section, after the contraindications and indication and use statement, and without any significant signal to alert the viewer to them. The overall effect of this webpage's presentation of risk information undermines the communication of the significant and potentially fatal risks associated with Recorlev and thereby misleadingly minimizes the risks associated with the use of Recorlev.

Conclusion and Requested Action

For the reasons discussed above, the webpages misbrand Recorlev within the meaning of the FD&C Act and make its distribution violative. 21 U.S.C. 352(a), (n); 321(n), 331(a). See 21 CFR 202.1 (e)(3)(i); (e)(5).

This letter notifies you of our concerns and provides you with an opportunity to address them. OPDP requests that Xeris cease any violations of the FD&C Act. Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Recorlev that contain representations like those described above, and explaining any plan for discontinuing use of such communications, or for ceasing distribution of Recorlev.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

[3] Ketoconazole is the racemic mixture from which levoketoconazole is derived.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 14 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 5013 under NDA 214133. Questions related to the submission of your response letter should be emailed to the OPDP RPM at CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ankur Kalola, PharmD, RAC
Regulatory Review Officer
Division of Advertising & Promotion Review 2
Office of Prescription Drug Promotion

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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